Single dose ciprofloxacin for treating gonococcal infections in men

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SUMMARY A single oral dose of ciprofloxacin 500 mg was used to treat five men with gonococcal urethritis and five men with gonococcal proctitis, and all were cured. In a subsequent study the dose of ciprofloxacin was reduced to 250 mg, and 54 men with 57 gonococcal infections (47 urethral, seven rectal, and three pharyngeal) were treated; of the isolates of *Neisseria gonorrhoeae*, four were penicillinase producing strains. All the patients were cured of gonococcal infection.

Urethral specimens from nine of the men with gonococcal urethritis yielded *Chlamydia trachomatis* before treatment. These organisms were isolated again from all these patients seven days after treatment, and from a further seven men who had been chlamydia negative before treatment.

It is concluded that a single oral dose of ciprofloxacin is an effective treatment for uncomplicated gonorrhoea, but is ineffective against *C trachomatis*. Of the 54 men given 250 mg ciprofloxacin, six (11%) showed minor abnormalities of liver function tests after treatment.

Introduction

Strains of *Neisseria gonorrhoeae* showing either decreased sensitivity to penicillin (minimum inhibitory concentrations (MICs) 0.12-2 µg/l) or β lactamase mediated resistance to penicillin are now causing serious concern.¹⁻³ Spectinomycin has been regarded as the best alternative to penicillin for treating acute gonococcal infections,⁴ but spectinomycin resistant strains of *N gonorrhoeae* have recently begun to emerge.^{5,6} The newer β lactamase stable cephalosporins, such as cefotaxime and ceftriaxone, are effective,^{7,8} but they cannot be given orally. There is therefore interest in non-β lactam antimicrobials that are active against *N gonorrhoeae* and can be administered orally.

Recent development of the 4-quinolone group of antibiotics has resulted in a series of compounds that are active against *N gonorrhoeae* and can be given orally. Some of these, such as acrosoxacin^{9,10} and norfloxacin,¹¹ have been evaluated clinically with good results. Felmingham *et al* have recently studied

the activity of 11 4-quinolone antibiotics against *N gonorrhoeae* in vitro, and noted that a new member of the group, ciprofloxacin, was the most active.¹² Furthermore, Ridgway *et al* have shown that ciprofloxacin is active against *Chlamydia trachomatis*;¹³ this might be of clinical importance in view of the common association of this organism with *N gonorrhoeae*.¹⁴

We report here the results of a dose ranging study of the effectiveness of single oral dose of ciprofloxacin against uncomplicated gonococcal infections of the male urethra, rectum, and pharynx, and against concomitant infection with *C trachomatis*.

Patients and methods

All the patients were studied in the department of genitourinary medicine at this hospital between November 1983 and February 1984. Men who had taken antibiotics during the preceding month were excluded, but otherwise patients were unselected. All gave informed consent to participating in the study.

After local and general examination had been performed, specimens were collected as follows. Urethral specimens were taken with a plastic loop; one was spread on to a slide for Gram staining, and another inoculated on to culture medium for the isolation of

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N gonorrhoeae. Next, an endourethral wire swab tipped with cotton wool was inserted 4-5 cm into the urethra and transferred to 2 ml culture medium for *C trachomatis*. Rectal and pharyngeal specimens were collected only from homosexual men. Rectal wall sampling was performed through a proctoscope, and wooden swabs tipped with cotton wool were used to collect material for Gram staining and for culture for *N gonorrhoeae* and *C trachomatis*. Material from the tonsillar beds and posterior pharyngeal wall was also collected with cotton wool tipped wooden swabs for culture for *N gonorrhoeae*. We examined first catch urine specimens from all patients for albumin and sugar and took blood samples for routine haematology and biochemistry tests and serological tests for syphilis.

We made a presumptive diagnosis of gonococcal urethritis or proctitis if intracellular Gram negative diplococci were seen in urethral or rectal smears, and these patients were treated immediately; the diagnosis of gonorrhoea was confirmed by culture in every case. In some patients with gonococcal proctitis, and all with pharyngitis, diagnosis depended on the results of culture; treatment was started when these were available. Treatment was with a single oral dose of ciprofloxacin, 500 mg in the first part of the study and 250 mg in the second. The drug was administered with a glass of water under supervision. Patients were asked to return for re-examination on days 3, 7, and 14 after treatment. At each attendance they were asked about symptoms and examined clinically, then urethral or rectal smears were taken for Gram staining and microscopy, specimens were taken from previously infected sites for culture for *N gonorrhoeae*, and first catch urine specimens were examined. Cell culture for *C trachomatis* was performed during the second and third examinations after treatment. Blood sampling for haematology and biochemistry tests was repeated on day 3.

Post gonococcal urethritis (PGU) was diagnosed if 10 or more polymorphonuclear leucocytes (PMNL) per high power field ($\times 100$ objective) were present in a Gram stained urethral smear, or if 15 or more PMNL per medium power field ($\times 40$ objective) were present in urinary sediment 10 or more days after treatment.

LABORATORY METHODS

Culture for *N gonorrhoeae* was performed on a modified Thayer-Martin medium,¹⁵ and isolates were identified by immunofluorescence and sugar fermentation. Cell culture for *C trachomatis* was performed using cycloheximide treated McCoy cells.¹⁶

Results

TREATMENT WITH 500 mg CIPROFLOXACIN

We treated 10 men who had confirmed gonococcal

infections with a single oral dose of ciprofloxacin 500 mg. Five of the men had urethral infections (one with a penicillinase producing strain of *N gonorrhoeae* (PPNG), and five had rectal infections. *N gonorrhoeae* was not isolated again from any of the men during follow up. One of the men with urethral gonococcal infections had a concomitant infection with *C trachomatis*, and this organism was isolated again at the first examination after treatment. None of the men with rectal infections yielded chlamydiae before or after treatment.

TREATMENT WITH 250 mg CIPROFLOXACIN

We treated 54 men who had confirmed gonococcal infections with a single oral dose of ciprofloxacin 250 mg. These men had a total of 57 infections with *N gonorrhoeae*; 47 urethral, seven rectal, and three pharyngeal. Of the 47 urethral infections, four were with PPNG strains and one with a non-PPNG strain that also showed reduced sensitivity to penicillin (MIC 2 $\mu\text{g/l}$). *N gonorrhoeae* was not isolated again from any of the 47 men with gonococcal urethritis. None of the seven rectal infections were with PPNG strains; *N gonorrhoeae* was not isolated again from any patient. Similarly, the three pharyngeal infections were with non-PPNG strains, and *N gonorrhoeae* was not isolated again from any patient.

EFFECT OF CIPROFLOXACIN ON CONCURRENT INFECTION WITH *C TRACHOMATIS*

Urethral specimens from nine (19%) of the 47 men with gonococcal urethritis yielded *C trachomatis* before treatment and seven days after treatment. In a further seven men, who were chlamydia negative before treatment, the organisms were isolated 7-14 days after treatment (table I).

TABLE I Urethral isolation of *Chlamydia trachomatis* before and after treatment of gonococcal urethritis with ciprofloxacin 25 mg

Isolation:		
Before	After	No of patients
Positive	Positive	9
Positive	Negative	0
Negative	Positive	7
Negative	Negative	30
Not performed		1

All the 16 men from whom *C trachomatis* was isolated after treatment with ciprofloxacin showed evidence of PGU. Of 30 patients without chlamydial infection after treatment, five (17%) developed

PGU. Of the whole group of 47 men treated for gonococcal urethritis, 21 (45%) developed PGU (table II).

TABLE II *Development of post gonococcal urethritis (PGU) after treatment of gonococcal urethritis with ciprofloxacin 250 mg*

<i>Chlamydia trachomatis</i> isolation after treatment	No of patients:	
	Total	Developing PGU
Positive	16	16
Negative	30	5
Test not performed	1	0
Total	47	21

None of the men with gonococcal infection of the rectum yielded *C trachomatis* either before or after treatment.

SIDE EFFECTS

Subjectively, ciprofloxacin was well tolerated. Two of the 10 men given 500 mg, and five of the 54 men given 250 mg complained of transient nausea. No haematological abnormalities were observed after treatment. In some patients results of liver function tests were normal on enrolment but abnormal after treatment. The tests performed were: serum total bilirubin concentration (normal range 3-20 $\mu\text{mol/l}$), alkaline phosphatase activity (30-115 IU/l), alanine transferase (SGPT) activity (up to 45 IU/l), aspartate transferase (SGOT) activity (up to 41 IU/l), γ -glutamyl transpeptidase (γ -GTP) activity (up to 65 IU/l), and concentrations of total proteins, albumen, and globulin. Of the 10 men given 500 mg ciprofloxacin, three showed raised SGOT activity up to 62 IU/l after treatment, with other liver function test results remaining normal. Abnormal test results were also seen in six (11%) of the 54 men given 250 mg ciprofloxacin (table III). Raised SGOT

TABLE III *Abnormal liver function test results in patients after treatment with ciprofloxacin 250 mg*

Abnormality after treatment	No of patients
None	48
Raised aspartate transferase (SGOT)	4
Raised SGOT	1
Raised alkaline phosphatase	1
Raised SGOT	
Raised bilirubin	

activity up to 68 IU/l was noted in four men after treatment, raised alkaline phosphatase activity to 271

IU/l in one, and raised bilirubin concentration to 26 $\mu\text{mol/l}$ in one patient. Other liver function test results were normal in all patients after treatment. Of the six patients with abnormal test results after treatment, four had normal test results two weeks later and the other two were lost to follow up.

Discussion

The uniform cure of men with uncomplicated gonococcal infections that we obtained with single oral dose of ciprofloxacin is encouraging, and at least in our clinic population there seems to be no need for a dose higher than the 250 mg that we used. In the study reported here, ciprofloxacin was equally effective against urethral and rectal infections. The cure of three pharyngeal infections is interesting, because these are often difficult to eradicate.¹⁷

In this dosage ciprofloxacin was ineffective against *C trachomatis*. In this respect it resembles other antimicrobial agents with good in vitro antichlamydial activity, such as thiamphenicol, minocycline, and rifampicin with erythromycin, none of which are effective against genital chlamydiae in single dosage.¹⁸⁻²⁰ No doubt this poor antichlamydial activity was largely the reason for PGU occurring in 45% of patients, a figure not very different from the incidences found in men treated with other antimicrobials in single dosage.^{18 20 21}

Ciprofloxacin was well tolerated subjectively, but liver function test results became abnormal after treatment in 11% of patients. The signs of hepatotoxicity were not pronounced, but they were there; this aspect will need close study in future clinical trials.

Our results show that ciprofloxacin may be a useful alternative to existing single dose treatment of gonorrhoea. The drug has the advantage of being a single oral regimen with freedom from major side effects. We suggest that it is studied further in both men and women. The effectiveness of a dose lower than the 250 mg that we used should also be studied.

References

1. Jackson DH, Jephcott AE. Penicillin sensitivity of gonococci. An evaluation of monitoring as an index of epidemiological control. *British Journal of Venereal Diseases* 1976;52:253-5.
2. McCutchan JA, Adler MW, Berrie JRH. Penicillinase producing *Neisseria gonorrhoeae* in Great Britain: alarming increase in incidence and recent development of endemic transmission. *Br Med J* 1982;285:337-40.
3. Brown S, Warnnissorn T, Biddle J, Panikabutra K, Traisupa A. Antimicrobial resistance of *Neisseria gonorrhoeae* in Bangkok: is single-dose treatment passé? *Lancet* 1982;ii:1366-8.
4. McCormack WM. Penicillinase-producing *Neisseria gonorrhoeae*. A retrospective. *N Engl J Med* 1982;307:438-9.
5. Ashford WA, Potts DW, Adams HJU, et al. Spectinomycin resistant penicillinase-producing *Neisseria gonorrhoeae*. *Lancet* 1981;ii:1035-7.

6. Ison CA, Littleton K, Shannon KP, Easmon CSF, Phillips I. Spectinomycin resistant gonococci. *Br Med J* 1983; **287**:1827-9.
7. Boakes AJ, Barrow J, Ekyn SJ, Phillips I. Cefotaxime for spectinomycin resistant *Neisseria gonorrhoeae*. *Lancet* 1981; **ii**: 96.
8. Handsfield HH, Murphy VL. Comparative study of ceftriaxone and spectinomycin for treatment of uncomplicated gonorrhoea in men. *Lancet* 1983; **ii**:67-70.
9. Handsfield HH, Judson FN, Holmes KK. Treatment of uncomplicated gonorrhoea with rosoxacin. *Antimicrob Agents Chemother* 1981; **20**:625-9.
10. Cohen AI, Rein MF, Noble RC. A comparison of rosoxacin with ampicillin and probenecid in the treatment of uncomplicated gonorrhea. *Sex Transm Dis* 1984; **11**:24-7.
11. Crider SR, Colby SD, Miller LK, Harrison WO, Kerbs SBJ, Berg SW. Treatment of penicillin-resistant *Neisseria gonorrhoeae* with oral norfloxacin. *N Engl J Med* 1984; **311**: 137-40.
12. Felmingham D, O'Hare MD, Gruneberg RN, Ridgway GL. The comparative activity of eleven quinolone antibiotics against penicillin-sensitive and penicillin-resistant non-beta lactamase producing and beta lactamase producing isolates of *Neisseria gonorrhoeae*. In: Spitzky KH, Korner K, eds. *Proceedings of the 13th international congress of chemotherapy*, 1983; **112**:27-30.
13. Ridgway GL, Mumtaz G, Gabriel FG, Oriel JD. The activity of ciprofloxacin and other 4-quinolones against *Chlamydia trachomatis* and *Mycoplasmas* in vitro. *Eur J Clin Microbiol* 1984; **3**:344-6.
14. Oriel JD, Ridgway GL. *Chlamydia trachomatis*: genital infection in men. *Br Med Bull* 1983; **39**:133-7.
15. Phillips I, Humphrey D, Middleton A, Nicol CS. Diagnosis of gonorrhoea by culture on a selective medium containing vancomycin, colistin, nystatin, and trimethoprim (VCNT). A comparison with Gram staining and immunofluorescence. *British Journal of Venereal Diseases* 1972; **48**:287-92.
16. Oriel JD, Ridgway GL. *Genital infection by Chlamydia trachomatis*. London: Arnold, 1982:114-5.
17. Anonymous. Gonorrhoea of the pharynx. *Br Med J* 1974; **ii**: 239-40.
18. Oriel JD, Ridgway GL, Goldmeier D, Felmingham DF. Treatment of gonococcal urethritis in men with a rifampicin-erythromycin combination. *Sex Transm Dis* 1982; **9**:208-11.
19. Oriel JD, Loo PS, Ridgway GL. Treatment of gonococcal infection in men with single dose thiamphenicol. *Sex Transm Dis* 1984; **11**:410-3.
20. Waterworth PM, Oriel JD, Ridgway GL, Subramanian S. Single dose minocycline in the treatment of gonococcal urethritis. *British Journal of Venereal Diseases* 1979; **55**:343-7.
21. Oriel JD, Ridgway GL, Reeve P, Beckingham D, Owen J. The lack of effect of ampicillin plus probenecid given for genital infection with *Neisseria gonorrhoeae* on associated infections with *Chlamydia trachomatis*. *J Infect Dis* 1976; **133**:568-71.